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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,238	07/03/2001	Lawrence P. Wackett	110.00230102	7517

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,238	WACKETT ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-10,17,18 and 24-27* is/are pending in the application.

4a) Of the above claim(s) *17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *7-10, 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants cancellation of claims 5 and 6 and amendment of claims 7, 9, 10, 24, 25 and 27, Paper No. 9, 11/26/2002, is acknowledged. Claims 7-10, 17, 18, and 24-27 are at issue and are present for examination. Applicants' arguments filed on 11/26/2002, Paper No. 9, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 17 and 18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7.

Information Disclosure Statement

Applicants filing of information disclosures, paper no. 10, filed 11/26/2002, is acknowledged. Those references considered have been initialed.

Claim Objections

Claims 26 and 27 are objected to because of the following informalities: Claims 26 and 27 each recite "...80% sequence identity to the amino acid sequence depicted at SEQ ID NO:2.". An amendment such as "...80% sequence identity to the amino acid sequence depicted **by** SEQ ID NO:2." Would be more appropriate.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a atrazine chlorohydrolase that comprises an amino acid sequence of SEQ ID NO: 2, does not reasonably provide enablement for any atrazine chlorohydrolase that comprises an amino acid sequence having greater than about 80% sequence identity to SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 9 and 24-27 are so broad as to encompass any atrazine chlorohydrolase protein or biologically active derivative thereof that maintains atrazine chlorohydrolase

activity, wherein said protein or biologically active derivative thereof comprises an amino acid sequence encoded by a DNA molecule that hybridizes to DNA complementary to DNA having the sequence shown in Figure 6 (SEQ ID NO:1), beginning at position 236 and ending at position 1655, under the stringency conditions of hybridization in buffer containing 0.25 M Na_2 HPO4, 7% SDS, 1% BSA, 1.0 mM EDTA at 65°C, followed by washing with 0.15 SDS and 0.1x SSC at 65°C (claims 9, 24 and 25) and any atrazine chlorohydrolase protein or biologically active derivative thereof, wherein said protein or biologically active derivative thereof comprises an amino acid sequence having greater than about 80% sequence identity to the amino acid sequence depicted at SEQ ID NO:2 (claims 26 and 27).

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of atrazine hydrolase proteins broadly encompassed by the claims, including those atrazine hydrolase proteins and biologically active derivatives thereof, which have merely at least greater then about 80% sequence identity to SEQ ID NOs:2. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that the atrazine chlorohydrolase having the amino acid sequence of SEQ ID NO: 2.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any atrazine chlorohydrolase and biologically active derivative thereof which maintains atrazine chlorohydrolase activity which has merely 80% amino acid sequence identity to SEQ ID NO: 2, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting atrazine chlorohydrolase activity; (B) the general tolerance of atrazine chlorohydrolases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a atrazine chlorohydrolase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain atrazine chlorohydrolase activity and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity)

are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those proteins or biologically active derivatives thereof, of the claimed genus having atrazine chlorohydrolase activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any atrazine chlorohydrolase with the above defined structural limitations. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the earlier 112 1st paragraph rejection based on the scope of enablement of claims 5, 6, 25 and 27, applicants have cancelled claims 5 and 6, amended claims 25 and 27 and traversed the rejection as it applied to amended claims 25 and 27. Previous to applicants amendment of claims 25 and 27, the claimed biologically active derivatives thereof had no structural or functional limitations. Upon applicants amendment these claims have been amended such that the biologically

active derivatives thereof claimed now are structurally and functionally limited. Applicants assert that claims 25 and 27 now define the claimed genus both structurally and functionally and that the previous rejection has been rendered moot by this amendment.

The rejection of claims 25 and 27 is maintained as well applied over claims 9, 24 and 26 on the basis that applicants disclosure is insufficient to enable the skilled worker to carry out the invention commensurate with the scope of the claims, as discussed above. Applicants submission that the application provides detailed guidance for identifying proteins and biologically active derivatives thereof, that fall within the scope of the claims, by the mere presentation of assays that one could use to determine if a biologically active derivative converts atrazine to hydroxyatrazine is not found persuasive. While such assays are necessary to determine if a biologically active derivative converts atrazine to hydroxyatrazine, the applicants disclosure gives no guidance such as (A) those regions of the protein structure which may be modified without effecting atrazine chlorohydrolase activity; (B) the general tolerance of atrazine chlorohydrolases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a atrazine chlorohydrolase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain atrazine chlorohydrolase activity and the fact that the relationship between the

sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable, it would require undue experimentation for one skilled in the art to arrive at the majority of those proteins or biologically active derivatives thereof, of the claimed genus having atrazine chlorohydrolase activity.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 7, 9, 10, and 24-27 are rejected under 35 U.S.C. 102(a) as being anticipated by Mandelbaum et al. (Applied and Environmental Microbiology, Vol 61, No. 4, pages 1451-1457, Apr. 1995, See IDS) as evidenced by DeSouza et al. (Journal of Bacteriology, Vol 178, No. 16, pages 4894-4900, Aug. 1996).

The rejection was stated in the previous office action. Applicants traverse this rejection on the basis that the disclosure by Mandelbaum et al. does not constitute "isolated and purified" as Mandelbaum et al. teach that crude cell extracts were prepared. Applicants submit that the previous action admits this in the characterization of Mandelbaum et al. at page 13 of the Action where it states that "one of ordinary skill in the art would have been motivated to further isolate and purify the atrazine chlorohydrolase that Mandelbaum et al. was in possession of...". Applicants further submit that as Mandelbaum et al. do not teach an isolated and purified protein that

converts atrazine to hydroxyatrazine, as the cited document does not teach each element of the claim.

Applicants arguments are not found persuasive, because as was previously stated, the preparation of cell extracts of *Pseudomonas* sp. as taught by Mandelbaum et al. constitutes the "isolation and purification" of those enzymes and proteins in the cell extract. This "isolated and purified" cellular extract taught by Mandelbaum et al. comprises the claimed atrazine chlorohydrolase and thus anticipates the rejected claims. This is further supported by applicants specification at page, 8, lines 22-25, in which applicants recite "As used herein, the terms 'isolated and purified' refer to in vitro isolation of a DNA molecule or protein from its natural cellular environment..." Clearly the extract taught by Mandelbaum et al. constitute isolated and purified as defined here, the removal of a protein from its natural cellular environment. Applicants submission that the previous action admits that the extract taught by Mandelbaum et al. does not constitute "isolated and purified" in the passage at page 13 of the Action where it states that "one of ordinary skill in the art would have been motivated to further isolate and purify the atrazine chlorohydrolase that Mandelbaum et al. was in possession of...", is taken out of context and does not support applicants position. The referred to passage was not a part of this rejection, but rather part of a separate rejection in which it was stated that "one of ordinary skill in the art would have been motivated to **further** isolate and purify the atrazine chlorohydrolase that Mandelbaum et al. was in possession of..." such that it could be immobilized on a support. The motivation to "further" isolate and purify the enzyme Mandelbaum et al. was in possession of, does not in any way reflect

on the state of the enzyme Mandelbaum et al. was in possession of with the exception that it was not in a such a state that it could be easily immobilized on a support. The cellular extract was still considered to be isolated and purified, it was only not isolated and purified enough.

Thus claims 7, 9, 10, and 24-27 are anticipated by Mandelbaum et al. as evidenced by DeSouza et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mandelbaum et al. (Applied and Environmental Microbiology, Vol 61, No. 4, pages 1451-1457, Apr. 1995, See IDS) and Kennedy (See IDS).

The rejection is stated in the previous office action.

Applicants traverse this rejection on the basis that the office has not established a *prima facie* case of obviousness based on a there conjecture that there is no motivation to combine the two documents used in the rejection. This argument is not persuasive, because as was previously stated, one of ordinary skill in the art would have been motivated to **further** (See above discussion under 102 rejection) isolate and purify the atrazine chlorohydrolase that Mandelbaum et al. was in possession of and

immobilize the enzyme on a support such that it could be used as system to remove the pesticide atrazine from the environment. The motivation to use the purified enzyme for such purposes comes from Mandelbaum et al. who teach that the presence of atrazine in soil needs to be removed and the identified activity provides a good means for doing so.

In response to applicants submission that Mandelbaum et al. does not teach or suggest an isolated and purified protein having the amino acid sequence shown in SEQ ID NO: 2, as was stated previously in the original rejection and the original 102 rejection, the enzyme Mandelbaum et al. was in possession of has the amino acid sequence of SEQ ID NO: 2. This was

In response to applicants submission that Mandelbaum et al. does not teach or suggest binding an isolated and purified protein to an immobilization support, this is suggested by Kennedy. As was previously stated, Kennedy teaches principles of enzyme immobilization, specifically the immobilization of hydrolases for use in waste treatment (see page 292). Applicants argue that Kennedy is not directed to the immobilization of enzymes present in crude cell extracts. This is acknowledged as it was previously pointed out that the original rejection it would be obvious to **further** isolate and purify the enzyme Mandelbaum et al. was in possession of. In response to applicants submission that Kennedy does not teach or suggest an isolated and purified protein having the amino acid sequence shown in SEQ ID NO: 2, as was stated previously in the original rejection, Mandelbaum et al. was in possession of the enzyme

having the amino acid sequence of SEQ ID NO: 2, and thus Mandelbaum et al. is relied upon for this.

Applicants arguments that there is no teaching of how to isolate and purify the claimed protein is not found persuasive. As discussed above, Mandelbaum et al. was in possession of the "isolated and purified" claimed protein, although it is acknowledged that the degree of purification of the protein that Mandelbaum et al. was in possession of was not such that it would be available for immobilization on a support. Hence one of skill in the art would be motivated to further isolate and purify the protein such that it could be attached to an immobilized support. The general knowledge in the art at the time of filing would have been sufficient to allow such purification of the protein of SEQ ID NO: 2. This in combination with the fact that Mandelbaum et al. was in possession of this protein and had to at least some extent isolated and purified the protein, as well as the fact that Mandelbaum et al. was in possession of an assay for the measurement of the protein's activity would have led one of skill in the art to the sufficiently purified protein, such that it could be immobilized on a solid support for its use in the waste treatment.

Thus claim 8 remains obvious over Mandelbaum et al. and Kennedy.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
February 14, 2003